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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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10/055,797

01/22/2002

David Beach

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EXAMINER

CHONG, KIMBERLY

ART UNIT

PAPER NUMBER

1635

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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3 MONTHS

04/17/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| | | | |
|------------------------------|-------------------------------|------------------------------|--|
| Office Action Summary | Application No. 10/055,797 | Applicant(s) BEACH ET AL. | |
| | Examiner Kimberly Chong | Art Unit 1635 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 83-108 and 111-124 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 83-108 and 111-124 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>01/26/2007</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 01/26/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 07/26/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 01/26/2007, claims 83-108 and 111-124 are pending in the application.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 112

The rejection of claims 83-108 and 111-124 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained for the reasons of record mailed 07/26/2006.

Applicant's arguments filed 01/26/2007 are acknowledged but are not found persuasive. Applicant asserts one can envision scenarios where there is cleavage at one end or both ends of a duplex region of a hairpin RNA that still results in a double stranded product.

While it is true that one can envision cleavage of a hairpin RNA at either end and the RNA would still be double stranded, what remains unclear, as stated in the rejection of record, is how a double stranded RNA is cleaved to *produce* a double stranded RNA product. A reasonable interpretation of the word "produce" could mean the RNA was not double stranded before cleavage. As such, it is unclear how the hairpin RNA, which is already double-stranded can be cleaved to further *produce* a double-stranded product.

Further, applicant has not addressed the further rejections with regard to claim 83. Specifically, the claim is drawn to a method of attenuation of expression of one or more target genes by a hairpin RNA which hybridizes to a target gene and reduces expression "if complementary to a target sequence". The method recites the hairpin RNA hybridizes to the target gene, therefore the hairpin RNA *is* complementary to the target gene because the only way a sequence can hybridize to another sequence is if the sequences are complementary. Claim 83 further recites the hairpin RNA reduces expression of said target gene in a manner dependent on the sequence of said complementary regions. It is unclear what "in manner dependent on the sequence" refers to when determining the reduction of expression of a target gene.

Applicant is reminded that a reply by the applicant or patent owner must be reduced to a writing which distinctly and specifically points out the supposed errors in the examiner's action and **must reply to every ground of objection and rejection in the prior Office action.** The reply must present arguments pointing out the specific

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distinctions believed to render the claims, including any newly added presented claims, patentable over any applied reference." See 37 C.F.R. 1.111(a)(2)(b)

Re: Claim Rejections - 35 USC § 103

The rejection of claims 83-87, 90-98, 102-108, 111-115 and 120-124 under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US Patent Number 6,506,559) and Ui-Tei et al. (FEBS Letters 2000) as further evidenced by Zhang et al. (Cell, 2004, vol. 118, pages 57-68) is maintained for the reasons of record mailed 01/26/2007.

The rejection of claims 83-98, 101-108, 111-124 under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US Patent Number 6,506,559), Ui-Tei et al. (FEBS Letters 2000) and Good et al. (Gene Therapy 1997) and as further evidenced by Zhang et al. (Cell, 2004, vol. 118, pages 57-68) is maintained for the reasons of record mailed 01/26/2007.

Applicant's arguments filed 01/26/2007 are acknowledged but are not found persuasive. Applicant traversed both of the rejections together and therefore the response below is in support of the rejections above.

Applicants assert the Fire et al. patent, the '559 Patent, does not teach attenuation of expression in a mammalian cell using a dsRNA. Applicants point to several references on pages 9-11 of the response filed 01/26/2007, namely Fire et al. and Wianny et al., as evidence that at the time of the filing date of the '559 Patent, attenuation of expression using dsRNA was not thought to work in mammalian cells. Applicants assert that Fire et al, in a reference post-filing of the '559 Patent, "essentially

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conceded that understanding the underlying mechanism of using dsRNA to induce sequence gene silencing in mammalian cells is important" and that this statement "supports the notion that he in fact did not understand such mechanism at the time."

Applicants further assert that the considerations raised by Fire et al. have "discouraged investigators from using RNAi in mammals" and point to a sole reference e.g. Wianny et al., as representative of the entire field of investigators discouraged from using RNAi in mammals before the instantly filed application. Further, applicants assert at the time of the '559 Patent, one would not have believed that one could attenuate gene expression of mammalian cells suspended in culture.

With respect to applicants assertion that the '559 patent does not teach RNAi in mammalian cells, it appears the general point of applicant's arguments above can be summarized to mean: because the '559 Patent did not exemplify RNAi in mammalian cells and only prophetically stated that such methods could be performed in mammalian cells, the '559 Patent does not anticipate the instantly claimed invention. This line of reasoning is not convincing. While it is noted and acknowledged that the '559 Patent does not provide a specific example of RNAi in mammalian cells, this is not required for a prior art reference to anticipate the claimed invention. The '559 Patent is presumed to be enabled and therefore teaches a method of attenuation of expression in mammalian cells using a dsRNA.

Further, applicant has made reference to a paragraph in the "Fire Article" (cited by applicant as pages 362-363) that is not consistent with the context of the invention of the method taught the '559 Patent, namely RNAi mediated gene silencing using dsRNA

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dsRNA in mammalian cells. Fire, a named inventor of the '559 Patent, comments on the possible PKR cellular effects of using RNAi when dsRNA is delivered a drug and this is not in the same context as eliciting RNAi mediated gene silencing in a cell using dsRNA. Moreover, the mere fact that Fire comments on the possible PKR effects of using dsRNA as a drug does not support the notion that Fire himself did not understand the mechanism of RNAi in mammalian cells. More importantly, this consideration has not discouraged investigators from using RNAi in mammalian cells, as stated by applicant. To the contrary, the field of RNAi is filled with investigators furthering the ideas set forth in the '559 Patent, as evidenced by Kreutzer et al. (WO 00/44895, of record in applicants IDS filed 07/01/2003) who aptly demonstrates RNAi using dsRNA in mammalian cells.

With respect to applicants assertion that one would not have believed that one could attenuate gene expression of mammalian cells suspended in culture, the '559 Patent clearly teach attenuation of expression of cells using dsRNA in 96 well microtiter plates i.e. in cells suspended in culture. Thus, as stated above, while it is noted and acknowledged that the '559 Patent does not provide a specific example of RNAi in mammalian cells suspended in culture, this is not required for a prior art reference to anticipate the claimed invention. As such, the above rejection is maintained for the reasons of record mailed 07/26/2007.

The rejection of claims 83-88, 90-108, 113-124 under 35 U.S.C. 103(a) as being unpatentable over Lieber et al. (U.S. Patent No. 6,130,092) and Tuschl et al. (US

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2002/0086356), Kennerdell et al. (Nature 2000) Fire et al. (US Patent Number 6,506,559) and Barber et al. (U.S. Patent No. 6,605,429) is maintained for the reasons of record mailed 01/26/2007.

Applicant's arguments filed 01/26/2007 are acknowledged but are not found persuasive. Applicants traverse the rejection on the grounds that both the Barber et al. and the Lieber et al. references relate to ribozymes and ribozymes do not contain sequences that both bind to the target sequence and are complementary to another sequence within the ribozyme as required by the instantly claimed invention. This is not convincing.

In response to applicant's arguments, it must be noted that the Lieber et al. reference was not relied upon for teaching sequences that both bind to the target sequence and are complementary to another sequence within the ribozyme. Lieber et al. was relied upon to teach identifying a gene responsible for a particular phenotype is crucial to any biological mechanism and the understanding of disease and teach the importance of the use of a library expression system that can identify genes that are specifically involved in producing a particular phenotype by knocking down intracellular expression. As such, one would have clearly been motivated to incorporate a siRNA in the library expression system to identify a functional gene since Tuschl et al. teach using siRNA is more efficient as compared to antisense and ribozyme and siRNAs have been shown to inhibit gene expression in a sequence-specific manner compared to antisense and ribozyme methodologies.

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Likewise, Barber et al. reference was not relied upon for teaching sequences that both bind to the target sequence and are complementary to another sequence within the ribozyme. Barber et al. was relied upon to teach that a hairpin RNA, an inhibitor nucleic acid, can be transcribed from an expression cassette and therefore it would have clearly been obvious to one of ordinary skill in the art to utilize inducible promoters in the expression cassette for transcribing a siRNA.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made and the rejection of record mailed 07/26/2006 is maintained.

Re: Claim Rejections - 35 USC § 102

The rejection of record of claims 83-88, 90-100, 102-108, 113-115, 120, 123-124 under 35 U.S.C. 102(e) as being anticipated by Barber et al. (U.S. Patent No. 6,605,429) as evidence by Hammond et al. (Nature 2000) is obviated in response to claim amendments filed 01/26/2007.

Re: Claim Rejections - 35 USC § 103

The rejection of record of claims 83-108, 113-115, 120, 123-124 under 35 U.S.C. 103(a) as being unpatentable over Barber et al. (U.S. Patent No. 6,605,429) in view of Good et al. (Gene Therapy 1997), Lipardi et al. (Cell 2001) in further view of Bennett et

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al. (U.S. Patent No. 5,998,148) and as evidence by Hammond et al. (Nature 2000) is obviated in response to claim amendments filed 01/26/2007.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

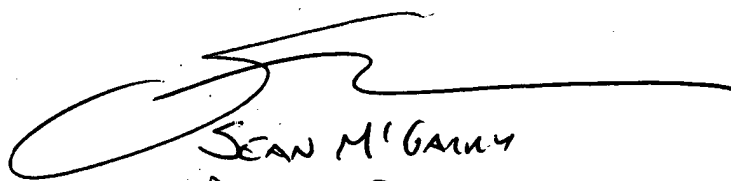
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.



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